

[54] **SYNERGISTIC NON-STEROIDAL ANTI-INFLAMMATORY COMPOUNDS AND COMPOSITIONS THEREOF**

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Related U.S. Application Data

[62] Division of Ser. No. 634,738, Jul. 26, 1984, Pat. No. 4,530,844.

[51] **Int. Cl.⁴** A61K 31/05; A61K 31/12

[52] **U.S. Cl.** 514/688; 514/731; 514/734

[58] **Field of Search** 514/688, 689, 734, 456, 514/731

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,145,444 3/1979 Hamazaki et al. 260/591
4,244,970 1/1981 Dewhirst 424/331

OTHER PUBLICATIONS

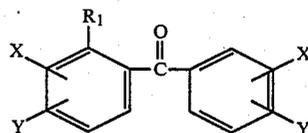
Dewhirst, Floyd Everett, "Eugenol, A Prototype Phenolic Prostaglandin Synthetase Inhibitor, its Anti-Inflammatory Activity, Its Effect on Sheep Vesicular Gland Cyclooxygenase, and Structure-Activity Relationships for Cyclooxygenase Inhibition by Sixty--Three Phenolic Compounds", PhD. Thesis, University

of Rochester 1978, available from University Microfilms International, Ann Arbor, Michigan.

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[57] **ABSTRACT**

Non-steroidal anti-inflammatory compositions comprising a compound of the formula:



wherein R₁ is H or OH; and X, Y, X¹ and Y¹ represent hydrogen or halogen, such as chloro, fluoro, bromo, or iodo radicals, lower alkyl radicals such as C₁-C₈ radicals, such as methyl, ethyl, propyl and butyl, lower haloalkyl radicals, such as trifluoro, trichloro or tribromo methyl radicals, and lower alkoxy radicals, such as C₁-C₈ radicals such as methoxy, ethoxy, propoxy, and octyloxy radicals or combinations thereof and the salts thereof, in combination with a compound selected from the group consisting of butylated hydroxytoluene, nordihydroguaiaretic acid and mixtures thereof, said combination being contained in a pharmaceutically acceptable carrier.

A method of treating pain and inflammation is also disclosed.

3 Claims, No Drawings

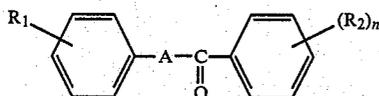
**SYNERGISTIC NON-STEROIDAL
ANTI-INFLAMMATORY COMPOUNDS AND
COMPOSITIONS THEREOF**

This is a divisional application of application with Ser. No. 634,738 filed July 26, 1984, now U.S. Pat. No. 4,530,844.

The present invention relates to combinations of non-steroidal anti-inflammatory compounds useful as active agents in the treatment of pain, inflammation, swelling and other related symptoms of mammals. This invention also relates to pharmaceutically acceptable compositions containing these actives as well as a method of treatment.

Non-steroidal anti-inflammatory compounds are well-known in the art. Examples of such compounds are aspirin, indomethacin, and phenylbutazone, to name a few. All of these have claims associated with them for the treatment of pain and inflammation in mammals. These compounds are known to cause side-effects, gastrointestinal disorders and headaches.

U.S. Pat. No. 4,145,444 to Hamazaki et al., discloses various non-carboxylic benzoyl derivatives as anti-inflammatory agents. In particular, those compounds disclosed have the formula:



wherein R₁ represents hydrogen, halogen, hydroxy, C₁₋₈ alkyl or C₁₋₈ alkoxy; R₂ represents hydrogen, halogen, hydroxy, vinyl, C₁₋₈ alkyl or C₁₋₈ alkoxy; A represents carbonyl, methylene or a single bond; and n is an integer of 1 to 4. It is preferred that R₂ be n-butyl substituted in the ortho or para position, and R₁ be hydrogen or halogen, e.g., compounds having the chemical name 4-n-butylbenzophenone or 4-n-butyl-2'-fluorobenzophenone.

U.S. Pat. No. 4,244,970 to Dewhirst discloses a method of treating inflammation and inhibiting prostaglandin synthesis by administering an effective amount of 2-hydroxybenzophenone and substitutes thereof. This patent discloses only those compounds having one hydroxy group located at the ortho position on at least one of the benzene rings.

The association between the production of prostaglandins in mammals and inflammation and pain is well documented. See Greaves and Sondergaard, *Journal of Investigative Dermatology* 72:59-63, 1979, where it was first demonstrated that prostaglandin activity was present in tissue fluid taken from inflamed human skin. Other investigators have subsequently reported that PGE₂ (prostaglandin E₂) concentrations in skin increase after exposure to ultraviolet (UVB) light and mediate a significant degree of redness and inflammation, particularly in the first 24 hours subsequent to exposure.

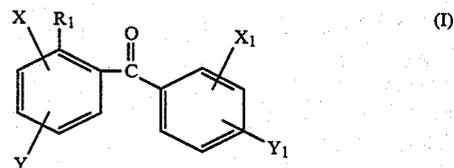
Without wishing to be bound by any one theory, it is believed that the inventive synergistic combination of compounds and compositions based thereon, are effective lipoxygenase and cyclooxygenase inhibitors. It is theorized that the effective inhibition of cyclooxygenase and lipoxygenase synthesis is the mechanism by which the novel compounds reduce and control pain and inflammation in mammals.

The literature has clearly shown that non-steroidal anti-inflammatory agents will reduce ultraviolet induced erythema by inhibiting the production of prostaglandin E₂ within the first 24 hour period subsequent to UVB exposure. See "Prostaglandins in the Skin," by Neal S. Penneys, published by Upjohn Co., 1980.

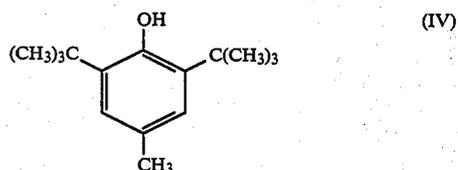
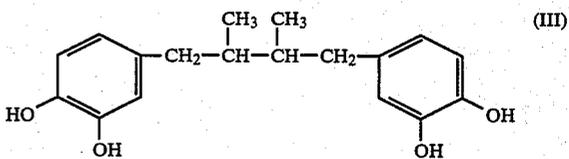
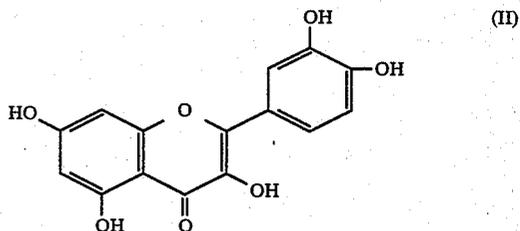
It is apparent that there is a need for effective, novel non-steroidal anti-inflammatory compounds which can be formulated into compositions using pharmaceutically acceptable carriers for topical, rectal, oral, perlingual or parenteral administration. The novel, instant compound fulfills this need.

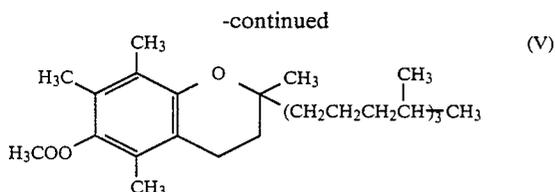
The instant invention concerns novel, synergistic combinations of compounds which act as anti-inflammatory compounds and which can be administered to mammals in therapeutically effective amounts for the relief of pain and inflammation, alone or in combination with a pharmaceutically acceptable carrier.

The inventive compositions contain a compound of the formula:



wherein R₁ is H or OH; and X, Y, X¹ and Y¹ represent hydrogen or halogen, such as chloro, fluoro, bromo, or iodo radicals, lower alkyl radicals such as C₁-C₈ radicals, such as methyl, ethyl, propyl and butyl, lower haloalkyl radicals, such as trifluoro, trichloro or tribromo methyl radicals, and lower alkoxy radicals, such as C₁-C₈ radicals such as methoxy, ethoxy, propoxy, and octyloxy radicals or combinations thereof and the salts thereof, in combination with a compound selected from the group consisting of the following compounds:





These compounds are commonly named:

- (II) Quercetin
- (III) Nordihydroguaiaretic acid (NDGA)
- (IV) Butylated hydroxytoluene (BHT)
- (V) Vitamin E acetate

Quercetin is a known bioflavonoid isolated from many plants, i.e., rhododendron cinnabarinum (see Merck Index, 8th Ed., Merck & Co., Inc., Rahway, N.J., 1968, p.899.) It has also been reported in the literature to inhibit lipoygenase formation in vitro (see "Biochemical Pharmacology," 32:2, 1983, Hope, W. C., et al.).

Nordihydroguaiaretic acid is a known antioxidant for fats and oils (see Merck Index, 9th Ed., 1976, p. 868). It has also been reported in the literature to strongly inhibit lipoygenase formation in vitro, and to a much lesser extent to inhibit prostaglandin formation (see Journal "Prostaglandins," 25:1, 1983, Casey, F. B. et al.).

BHT is a known antioxidant for foods, cosmetics, etc. (see Merck Index, 8th Ed., 1968, p. 179) as well as an inhibitor of lipoygenase in vitro (see Journal "Prostaglandins," 14:2, 1977, Panganamala, R. V., et al.).

Vitamin E acetate is a non-oxidizable form of vitamin E used for the same indications as vitamin E (see Merck Index 9th Ed., p. 290). Additionally, vitamin E acetate has been reported as inhibiting platelet lipoygenase in vitro (see Journal "Research Communications for Chemical Pathology & Pharmacology," 28:2, May, 1980, Givelu, E. T., et al.).

Compounds (II)-(V) above have not been reported as being anti-inflammatory compounds alone or in combination with those compounds of structure (I) above. The instant invention relates specifically to the synergistic anti-inflammatory properties achieved when a compound from structure (I) above is used with one or more compounds selected from structures II, III, IV and V above. Preferably, the anti-inflammatory compositions of this invention comprise 2-hydroxy-4-methoxy-benzophenone in combination with a compound selected from the group consisting of vitamin E acetate, butylated hydroxytoluene (BHT), quercetin, nordihydroguaiaretic acid (NDGA) and mixtures thereof. This combination may be administered alone, but is preferably administered in a pharmaceutically acceptable carrier as a remedy for pain inflammation and other related symptoms in mammals.

The instant combination of compounds is generally used in a therapeutically effective amount, but when contained in a pharmaceutically acceptable carrier or composition, is generally present in about 0.05% to about 50%, preferably about 0.1% to about 30% and most preferably about 0.1% to about 5% by weight of the total composition, inclusive of the carrier.

Those compositions most preferred have 2-hydroxy-4-methoxybenzophenone in amounts of about 0.05% to about 5% in combination with 0.01% to about 3% of BHT, NDGA or quercetin, or about 0.05% to about 5% of 2-hydroxy-4-methoxybenzophenone in combina-

tion with about 0.01% to about 1.0% of vitamin E acetate.

The instant compositions are intended for use in the treatment of a variety of inflammatory problems and diseases including systemic diseases such as arthritis and the like. Dosage forms include topical creams, pastes, ointments, gels, lotions and the like, for direct application to the inflamed area. Oral dosage forms include, but are not limited to capsules, tablets, solutions, syrups, powders and the like. Rectal, perlingual and parenteral dosage forms are also contemplated.

The preferred dosage form is a topical lotion comprising the inventive compounds or mixtures thereof in a pharmaceutically acceptable carrier. Illustrations of useful carriers include ethanol and other lower alkyl alcohols, polyalcohols, mineral oils, vegetable oils, petrolatum, glycerine, nonionic surfactants, water and the like, as well as mixtures of these. Compositions comprising from about 0.05% to about 50% by weight and preferably about 0.1% to about 5% of the inventive combination of compounds in the above carriers have been found particularly effective in the treatment of inflammation of the skin, commonly known in the art as erythema.

The active anti-inflammatory compound of the instant invention can be applied together with other anti-inflammatory agents, analgesics, thrombus dissolving agents, thrombus inhibiting agents, antibiotics and the like.

In the case where the active compound is incorporated in a pharmaceutical composition, other common materials such as lubricants, humectants, surfactants, waxes, emulsifiers, thickeners, emollients, preservatives, demulcents, perfumes, coloring additives and the like may be added. These, of course, are not critical to the invention and their amounts can be varied and balanced to meet the desired properties of the overall composition, which is discoverable by routine experimentation by one skilled in the art.

The instant composition may include materials that serve as occlusives in that they hold moisture against the surface of the skin. Suitable occlusive compounds include cetyl alcohol, cetyl palmitate, petrolatum, mineral oil and the like. These materials are generally present in topical compositions, for example, in amounts of about 1% to about 25% by weight of the composition and preferably in amounts of about 2% to about 10%.

A variety of materials may be utilized as emulsifiers, including high molecular weight polyethylene glycols, fatty alcohols such as stearyl alcohol and myristyl alcohol and the like. These materials are generally present in amounts of about 0.1% to about 15% by weight of the composition and preferably in amounts of about 1% to about 10%.

Suitable emollients for use in the instant compositions containing the novel anti-inflammatory compounds include fatty acid esters such as cetyl palmitate, diisopropyl adipate, isopropyl isostearate, isostearyl isostearate and mixtures thereof, to name a few. Generally they are present in topical compositions in amounts of about 0.1% to about 20% by weight of the composition and preferably in amounts of about 1% to about 10%.

Suitable humectants may be any of those well known in the art. Examples of useful humectants include glycerin, propylene glycol, polyethylene glycol, polyhydric alcohols and mixtures thereof, to name a few. Preferably, glycerin is used. These materials may be incorporated in the inventive anti-inflammatory compositions

in amounts of about 0.1% to about 30% by weight of the composition and preferably in amounts of about 3% to about 20%.

Numerous surfactants, and preferably non-ionic surfactants, may be added for their intended purpose. Among those preferred are polyalkanolamines such as triethanolamine, polyethylene glycol stearate, polyethylene glycol laurate, polyoxyethylene and polyoxypropylene compounds, e.g. as derivatives of sorbitan and fatty alcohol esters, fatty acid esters of polyhydric alcohols and amine oxides; anionic surfactants, such as alkyl carboxylates, acyl lactylates, sulfuric acid esters (e.g. sodium lauryl sulfate), ester-linked sulfonates, and phosphated ethoxylated alcohols; cationic surfactants, such as monoalkyl and dialkyl quaternary ammonium salts, amidoamides and aminimides. These various surfactants, when compatible, can be added as mixtures to the instant compositions and are generally present in amounts of about 0.1% to about 15% by weight of the composition.

Lubricating agents may be used when desired in the instant compositions. They include silicone oils or fluids such as substituted and unsubstituted polysiloxanes, e.g. dimethyl polysiloxane, also known as dimethicone, is particularly useful when the composition is to be used as a topical preparation. The lubricating agents, when incorporated in a topical composition, are generally present in amounts of about 0.1% to about 30% by weight of the composition and preferably in amounts of about 1% to about 10%. Other lubricating agents well known to the tableting and capsule art may be used when the dosage form is a tablet, pill or capsule. These lubricating agents are primarily to aid in formation of tablets.

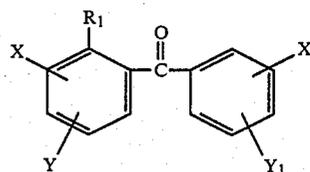
Preservatives such as alkyl and aryl parabens and substituted phenols are also useful additives. Examples of the preferred parabens are the methyl, propyl and butyl parabens useful in ranges of 0.1 to about 0.25%. In a preferred embodiment, a combination of methyl, propyl and butyl paraben may be used in the respective ranges of about 0.1% to about 0.25%, 0.02% to about 0.2% and 0 to about 0.05%. Examples of the useful substituted phenols include chloro-substituted phenoxy phenols, such as 5-chloro-2-(2,4-dichloro-phenoxy) phenol, hexacholophene, triclosan and dichlorophene, among others.

Other useful preservatives include mercury derivatives, such as phenylmercuric acetate; quarternaries, such as benzethonium chloride, benzalkonium chlorides and cetyl trimethyl ammonium bromide; acids, such as sorbic acid; and a variety of other preservatives such as Kathon CG, a trademark of Rohm & Haas Co. which comprises a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one.

Other conventional additives may be utilized, such as fragrance oils, thickeners, emulsifiers and other additives. For example, in the case of a topical lotion, thickeners for viscosity adjustment would include xanthan gum, sodium stearyl sulfate, and materials of that type.

The foregoing recitation of materials is presented for purposes of illustration and not limitation, it being understood that a variety of equivalent materials would all function in the capacities set forth above.

The instant invention also includes a method of treatment for inflammation, pain and related symptoms whereby a mammal is administered a therapeutically effective amount of a composition comprising a compound of the formula:



wherein R_1 is H or OH; and X, Y, X^1 and Y^1 represent hydrogen or halogen, such as chloro, fluoro, bromo, or iodo radicals, lower alkyl radicals such as C_1 - C_8 radicals, such as methyl, ethyl, propyl and butyl, lower haloalkyl radicals, such as trifluoro, trichloro and tribromo methyl radicals, and lower alkoxy radicals, such as C_1 - C_8 radicals such as methoxy, ethoxy, propoxy, and octyloxy radicals or combinations thereof and the salts thereof, in combination with a compound selected from the group consisting of nordihydroguaiaretic acid, butylated hydroxytoluene, quercetin, vitamin E acetate and mixtures thereof.

The invention will be further appreciated by the following example which is intended to illustrate an embodiment of the instant invention. All percentages throughout the specification are by weight of the total composition unless otherwise indicated.

EXAMPLE

This example is designed after the guinea pig model of Snyder, Journal of Investigative Dermatology, 64:322-25, 1975, and demonstrates that skin inflamed by ultraviolet light (U.V.B.) can be effectively therapeutically treated using a compound of the instant invention. Additionally, this example demonstrates that the instant combination of compounds when applied topically in a dermatological preparation is effective in inhibiting the production of cyclooxygenase & lipoxygenase are believed to be responsible for the inflammation.

The dorsal surface of a male albino guinea pig was shaved with a standard animal clipper (#40 head), depilated with a commercially available thioglycolate based depilatory product, rinsed with tap water and dried. The animal was immobilized in a standard head stock and irradiated for 30 minutes. This period of irradiation was found to be equivalent to 3 MED's. An MED (minimum erythema dose) is the minimal amount of U.V.B. radiation required to produce sunburn 24 hours subsequent to exposure. The U.V.B. light source was a bank of Westinghouse FS-40 lamps.

Immediately after irradiation, the animal's exposed dorsal surface was delineated with a black marking pen into treatment sites. Individual sites were treated with 3% solutions of BHT, NDGA, quercetin or 2-hydroxy-4-methoxy benzophenone. Other sites were individually treated with a 1% solution of vitamin E acetate. Still other areas were treated with combinations comprising 3% 2-hydroxy-4-methoxybenzophenone and one of the following: 1% vitamin E acetate, 3% BHT, 3% NDGA or 3% quercetin (all in solution). The sites were then visually evaluated for lack of erythema (blanching) at 1, 5 and 24 hours post-treatment by a trained, double-blinded observer. The results, as described below, were based on the following scale:

0 - No Blanching
 1 - Barely Detectable Blanching
 2 - Moderate Blanching
 3 - Severe Blanching
 4 - Complete Blanching (no erythema)

The results are tabulated below:

Agent	Vehicle	Blanching Score		
		1 hr.	5 hrs.	24 hrs.
2-hydroxy-4-methoxybenzophenone (3%) ^(a)	ETOH*	2	2	0
Vitamin E acetate (1%)	"	0	0	0
Vitamin E acetate/2 hydroxy-4-methoxybenzophenone (1%/3%)	"	2+	3	0
2 hydroxy-4-methoxybenzophenone (3%)	P.V.**	2	2	0
BHT (3%)	"	0	0	0
2 hydroxy-4-methoxybenzophenone/BHT (3%/3%)	"	3	2	0
2 hydroxy-4-methoxybenzophenone (3%)	P.V.**	2	2	1
Quercetin (3%)	"	1	2	0
Quercetin/2-hydroxy-4-methoxybenzophenone (3%/3%)	"	2	1+	1+
2 hydroxy-4-methoxybenzophenone (3%)	P.V.**	2+	1	0
NDGA (3%)	"	0	0	0
NDGA/2 hydroxy-4-methoxybenzophenone (3%/3%)	"	3	2+	0

*Ethanol.

**Propylene glycol:Ethanol:N,N-dimethylacetamide (19:19:2).

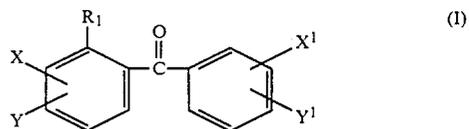
^(a)Percents on a weight/weight basis of total product.

These results indicate that post-irradiation application of the combinations of the instant invention inhibits prostaglandin production as indicated by the reduction of inflammation evidenced by blanching. These combinations of compounds act in a synergistic manner as evidenced by above data showing antiprostaglandin effect that is superior to the sum of the antiprostaglandin effects of their individual components.

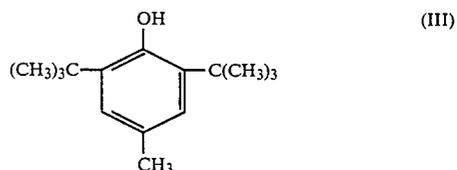
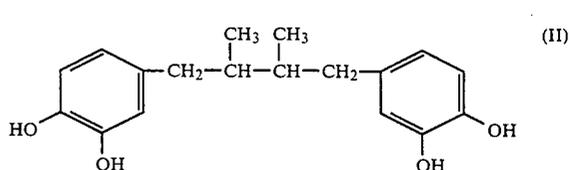
The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the claims.

What is claimed is:

1. An anti-inflammatory composition for use in the treatment of mammals comprising about 0.05% to about 5% of a compound of the formula:

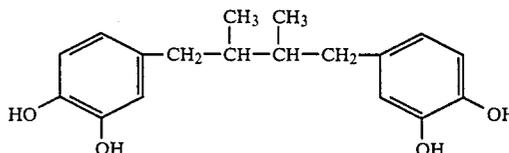


where R¹ is H or OH, X, Y, X¹ and Y¹ represent hydrogen or halogen radicals, lower alkyl radicals C₁-C₈, lower haloalkyl radicals, or lower alkoxy radicals C₁-C₈, the salts there of and combinations thereof; in combination with 0.01 to about 3% of one or more of the following compounds:

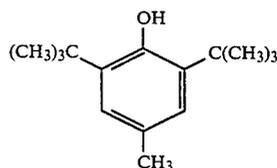


said combination of compounds being present in a pharmaceutically acceptable carrier wherein the combination is present in amounts of about 0.5% to about 50% by weight of the total composition including carrier.

2. The composition of claim 1 wherein there is present about 0.05% to about 5% of 2-hydroxy-4-methoxybenzophenone and about 0.01% to about 3% of the compound having the formula:



3. The composition of claim 1 wherein there is present about 0.05% to about 5% of 2-hydroxy-4-methoxybenzophenone and about 0.01% to about 3.0% of the compound having the formula:



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